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DOI:

[10.1186/s12968-016-0301-y](https://doi.org/10.1186/s12968-016-0301-y)

*Document Version*

Publisher's PDF, also known as Version of record

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*Citation for published version (APA):*

Kato, S., Nakamori, S., Roujol, S., Delling, F. N., Akhtari, S., Jang, J., Basha, T., Berg, S., Kissinger, K. V., Goddu, B., Manning, W. J., & Nezafat, R. (2016). Relationship between native papillary muscle T1 time and severity of functional mitral regurgitation in patients with non-ischemic dilated cardiomyopathy. *Journal of Cardiovascular Magnetic Resonance*, 18(1), [79]. <https://doi.org/10.1186/s12968-016-0301-y>

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RESEARCH

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# Relationship between native papillary muscle $T_1$ time and severity of functional mitral regurgitation in patients with non-ischemic dilated cardiomyopathy

Shingo Kato<sup>1,3</sup>, Shiro Nakamori<sup>1</sup>, Sébastien Roujol<sup>4</sup>, Francesca N. Delling<sup>1</sup>, Shadi Akhtari<sup>1</sup>, Jihye Jang<sup>1</sup>, Tamer Basha<sup>1,5</sup>, Sophie Berg<sup>1</sup>, Kraig V. Kissinger<sup>1</sup>, Beth Goddu<sup>1</sup>, Warren J. Manning<sup>1,2</sup> and Reza Nezafat<sup>1\*</sup>

## Abstract

**Background:** Functional mitral regurgitation is one of the severe complications of non-ischemic dilated cardiomyopathy (DCM). Non-contrast native  $T_1$  mapping has emerged as a non-invasive method to evaluate myocardial fibrosis. We sought to evaluate the potential relationship between papillary muscle  $T_1$  time and mitral regurgitation in DCM patients.

**Methods:** Forty DCM patients ( $55 \pm 13$  years) and 20 healthy adult control subjects ( $54 \pm 13$  years) were studied. Native  $T_1$  mapping was performed using a slice interleaved  $T_1$  mapping sequence (STONE) which enables acquisition of 5 slices in the short-axis plane within a 90 s free-breathing scan. We measured papillary muscle diameter, length and shortening. DCM patients were allocated into 2 groups based on the presence or absence of functional mitral regurgitation.

**Results:** Papillary muscle  $T_1$  time was significantly elevated in DCM patients with mitral regurgitation ( $n = 22$ ) in comparison to those without mitral regurgitation ( $n = 18$ ) (anterior papillary muscle:  $1127 \pm 36$  msec vs  $1063 \pm 16$  msec,  $p < 0.05$ ; posterior papillary muscle:  $1124 \pm 30$  msec vs  $1062 \pm 19$  msec,  $p < 0.05$ ), but LV  $T_1$  time was similar ( $1129 \pm 38$  msec vs  $1134 \pm 58$  msec,  $p = 0.93$ ). Multivariate linear regression analysis showed that papillary muscle native  $T_1$  time ( $\beta = 0.10$ , 95 % CI: 0.05–0.17,  $p < 0.05$ ) is significantly correlated with mitral regurgitant fraction. Elevated papillary muscle  $T_1$  time was associated with larger diameter, longer length and decreased papillary muscle shortening (all  $p$  values  $< 0.05$ ).

**Conclusions:** In DCM, papillary muscle native  $T_1$  time is significantly elevated and related to mitral regurgitant fraction.

## Background

Functional mitral regurgitation, a consequence of left ventricular (LV) remodeling despite normal mitral valve structure, is one of the common and severe complications in non-ischemic dilated cardiomyopathy patients (DCM) [1–4]. It has been reported that the annular enlargement and mitral leaflet tethering by the displacement of papillary muscles due to LV dilatation are the main mechanisms of

functional mitral regurgitation [5]. To date, little is known regarding the relationship between papillary muscle function and mitral regurgitant fraction in DCM patients.

Native (non-contrast)  $T_1$  mapping has emerged as a cardiovascular magnetic resonance (CMR) method to assess LV diffuse myocardial fibrosis [6]. Studies have shown that native  $T_1$  mapping detects diffuse myocardial abnormalities in hypertrophic cardiomyopathy and DCM [7–9]. The extent of myocardial damage by acute myocardial infarction can also be accurately assessed by native  $T_1$  mapping [10]. Diffuse myocardial abnormalities in patients with cardiac amyloidosis [11] and Anderson-Fabry disease [12, 13]

\* Correspondence: rnezafat@bidmc.harvard.edu

<sup>1</sup>Department of Medicine (Cardiovascular Division), Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA

Full list of author information is available at the end of the article



can be assessed by native  $T_1$  mapping. However, data is lacking regarding native  $T_1$  mapping of papillary muscles in these myopathies, including DCM.

Therefore, we sought to examine papillary muscle native  $T_1$  mapping in DCM and to investigate the relationship between papillary muscle native  $T_1$  time and functional mitral regurgitation in this population.

## Methods

### Study subjects

Forty DCM patients ( $55 \pm 13$  years; 31 male) and 20 healthy adult control subjects ( $54 \pm 13$  years; 13 male) free of any cardiovascular diseases were studied. All participants were in sinus rhythm at the time of scan.

### CMR acquisition

CMR was performed using a 1.5 T system and a 32-channel cardiac phased array receiver coil (Achieva, Philips Healthcare, Best, The Netherlands). Cine CMR, phase contrast images of the ascending aorta,  $T_1$  mapping and 3 dimensional late gadolinium enhancement (LGE) were obtained in all participants [14].  $T_1$  mapping was performed using a free-breathing slice-interleaved  $T_1$  (STONE) sequence [15].

Electrocardiogram monitoring leads were positioned with the subject in the supine position. Vertical and horizontal LV long-axis cine images were acquired using a steady-state free precession (SSFP) sequence. LV volumes and mass were calculated from an LV short-axis stack of cine images extending from the apex to the base (repetition time (TR), 3.3 ms; echo time (TE), 1.6 ms; flip angle (FA),  $60^\circ$ ; field-of-view (FOV),  $320 \times 320$  mm; acquisition matrix,  $128 \times 128$ ; slice thickness, 8 mm; gap, 2 mm) [16]. Phase contrast images were acquired perpendicular to the proximal ascending aorta to quantify blood flow by following parameters (TR, 15 ms; TE, 6.5 ms; FA,  $30^\circ$ ; velocity encoding, 300 cm/s; FOV,  $320 \times 320$  mm; acquisition matrix,  $288 \times 288$ ; number of phases per cardiac cycle, 36). STONE native  $T_1$  mapping was acquired in the short axis during free-breathing using slice-tracking with a balanced SSFP readout (5 slices, TR/TE = 2.8/1.4 msec, flip angle =  $70^\circ$ , FOV =  $360 \times 351$  mm, voxel size =  $2.1 \times 2.1$  mm, slice thickness = 8 mm, TFE factor = 86, SENSE factor = 2).

Fifteen minutes after the injection of 0.2 mmol/kg gadobenate dimeglumine, LGE images were acquired using a 3 dimensional sequence [14] with following parameters (TR, 5.3 ms; TE, 2.1 ms; FA,  $70^\circ$ ; FOV,  $320 \times 320 \times 125$  mm<sup>3</sup>; acquisition matrix,  $224 \times 224 \times 23$ ; spatial resolution,  $1.4 \times 1.4 \times 1.5$  mm; reconstruction resolution,  $0.6 \times 0.6 \times 0.8$  mm).

### Image analysis

Data were analyzed using a commercial workstation (Extend MR Workspace, version 2.3.6.3, Philips Healthcare). To determine LV mass, epi- and endocardial LV borders were

manually traced on the short axis images. LV mass was calculated as the sum of the myocardial volume multiplied by the specific gravity (1.05 g/mL) of myocardial tissue [17]. Left atrial (LA) volume was calculated using biplane area length method [18]. Papillary muscle morphology (diameter, length and shortening), anterior and posterior mitral leaflet length, mitral annulus diameter (both in 2 chamber and 4 chamber views) and tenting height were measured by cine CMR (Fig. 1). Papillary muscle shortening was calculated as follows.

#### *Papillary muscle shortening (%)*

$$= \frac{[\text{maximum papillary muscle length (mm)} - \text{minimum papillary muscle length (mm)}]}{\text{maximum papillary muscle length (mm)}} \times 100$$

Aortic blood flow was determined using the semi-automated algorithms [19]. Phase offset correction was performed as described previously [20]. Mitral regurgitation volume was calculated as the difference between the LV stroke volume and ascending aorta forward flow [21]. Mitral regurgitant fraction was calculated as follows.

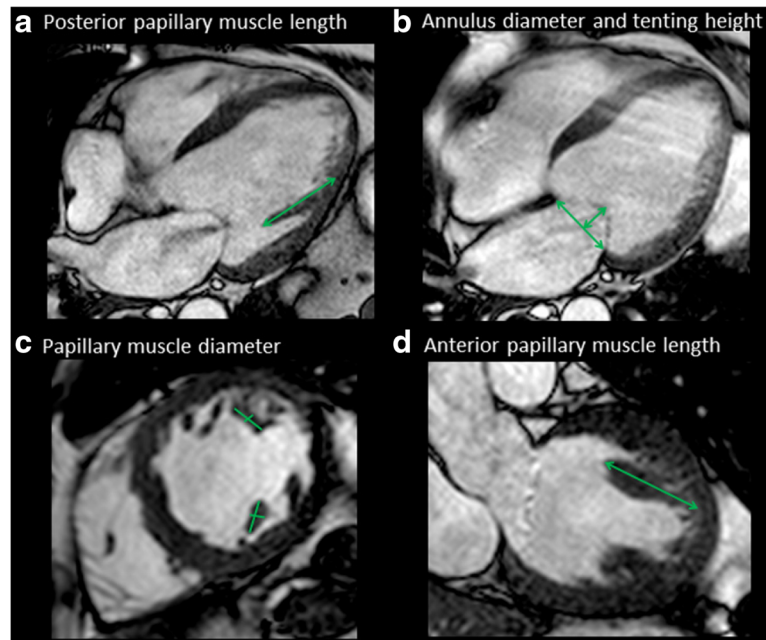
#### *Mitral regurgitant fraction (%)*

$$= \frac{[\text{LV stroke volume (mL)} - \text{ascending aorta forward flow (mL)}]}{\text{LV stroke volume (mL)}} \times 100$$

For calculating papillary muscle native  $T_1$  time, both anterior and posterior papillary muscles were manually traced on custom software (MediaCare, Boston, MA, USA) (Fig. 2). For calculating LV native  $T_1$  time, the three short axis LV slices were then divided into 6 segments for base and mid slices, 4 segments for apical slice using the anterior right ventricular-LV insertion point as reference. The 16 segment model was used to assess native  $T_1$  time in each segments. The native  $T_1$  time from all the segments was averaged to calculate each subjects LV  $T_1$  time. Motion correction was performed using the adaptive registration of varying contrast-weighted images for improved tissue characterization (ARCTIC) approach [22]. To evaluate inter-observer variability, measurements of papillary muscle native  $T_1$  time from 10 DCM patients and 10 healthy adult controls were independently taken by two observers. One of the two observers measured papillary muscle native  $T_1$  time twice to assess intra-observer variability. The time delay between two read for intra-observer variability was 1 month. Visual assessment was performed to evaluate for LV and papillary muscle scar on LGE.

### Statistical analysis

Data were analyzed using SPSS software (version 17.0, SPSS, Inc., Chicago, IL, USA) and MedCalc for Windows (version 14.8.1, MedCalc Software, Ostend, Belgium). Continuous values are presented as mean  $\pm$  standard deviation (SD). Categorical values are expressed as



**Fig. 1** Measurement of papillary muscle, mitral annulus and tenting height. (a) posterior papillary muscle length measurement, (b) mitral annulus and tenting height measurement, (c) papillary muscle diameter measurement, (d) anterior papillary muscle length measurement

number (%). DCM patients were divided into 2 groups based on the presence or absence of mitral regurgitation. To assess the difference between 3 groups (DCM patients with mitral regurgitation,  $n = 22$ ; DCM patients without mitral regurgitation,  $n = 18$ ; control subjects,  $n = 20$ ), one-way analysis of variance (ANOVA) with Tukey's correction was used for continuous variables. Chi-square test was used to

assess the difference for categorical variables. Bland and Altman plot [23], coefficient of variation (CV) were used to evaluate intra- and inter-observer variability for measuring papillary muscle native  $T_1$  time. Repeatability coefficients were calculated as 1.96 times the SD of the differences on the Bland-Altman plots. Spearman's correlation coefficient was calculated to evaluate relationship between papillary muscle  $T_1$  time and papillary muscle morphology (diameter, length and shortening). Multivariate linear regression analysis was performed to identify the determinants of mitral regurgitation severity in DCM patients. Variables with  $p$ -value  $< 0.05$  in the univariable analysis were included in the multivariable linear regression analysis (stepwise method).  $P$  value  $< 0.05$  was considered as statistically significant.

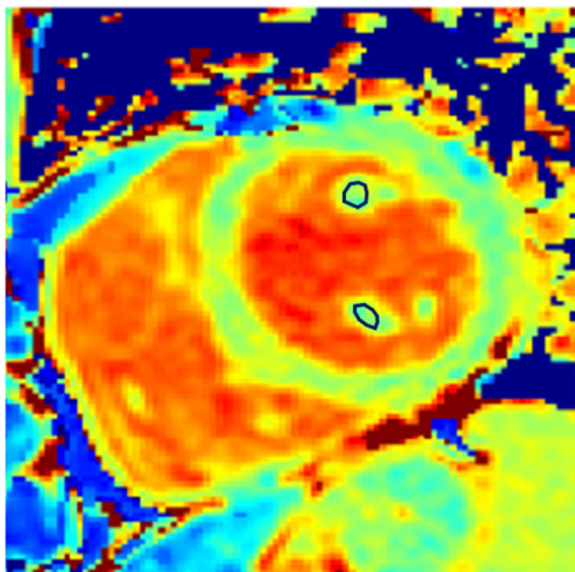
## Results

### Patients' characteristics

Table 1 summarizes the clinical characteristics of study subjects. There was no significant difference in gender, age, body mass index, systolic and diastolic blood pressure, heart rate between 3 groups. Information of medical therapy was also shown in Table 1.

### Cine MRI and LGE findings

Table 2 summarizes CMR findings. LV end-diastolic volume index, LV end-systolic volume index, LV mass index were significantly higher (all  $p < 0.05$ ) in DCM patients in comparison to controls. Stroke volume index and LV ejection fraction were significantly decreased ( $p < 0.05$ )



**Fig. 2** Measurement of native  $T_1$  time of papillary muscles. Location of anterior and posterior papillary muscle  $T_1$  measurement. Blue circle represents region of interest for  $T_1$  measurement. ROI region of interest

**Table 1** Characteristics of study subjects

	DCM MR (+), N = 22	DCM MR (-), N = 18	Controls, N = 20	* P-value DCM MR (+) vs DCM MR (-)	* P-value DCM MR (+) vs Controls	* P-value DCM MR (-) vs Controls
Demographics						
Male, %	15 (68 %)	16 (89 %)	13 (65 %)	0.12	0.83	0.083
Age, years	52 ± 16	58 ± 13	54 ± 13	0.32	0.98	0.44
Height, cm	176 ± 9	175 ± 8	172 ± 8	0.99	0.41	0.52
Body weight, kg	93 ± 20	86 ± 15	79 ± 15	0.47	0.10	0.67
BMI, kg	30 ± 7	28 ± 6	27 ± 4	0.51	0.21	0.86
BSA, m <sup>2</sup>	2.1 ± 0.3	2.0 ± 0.2	1.9 ± 0.2	0.58	0.10	0.57
SBP, mmHg	116 ± 14	119 ± 17	119 ± 12	0.80	0.70	0.99
DBP, mmHg	70 ± 11	74 ± 14	71 ± 10	0.53	0.70	0.59
Heart rate, bpm	76 ± 12	73 ± 12	68 ± 14	0.77	0.14	0.47
Medications						
Aspirin	7 (32 %)	7 (39 %)	-	0.64	-	-
ACE/ARBs	18 (82 %)	16 (89 %)	-	0.38	-	-
Calcium channel blockers	2 (9 %)	2 (11 %)	-	0.83	-	-
Beta blockers	17 (77 %)	14 (78 %)	-	0.97	-	-
Diuretics	11 (50 %)	7 (39 %)	-	0.48	-	-
Aldosterone inhibitors	2 (9 %)	1 (6 %)	-	0.67	-	-
Statin	9 (41 %)	9 (50 %)	-	0.57	-	-
Warfarin	5 (8 %)	2 (11 %)	-	0.90	-	-

\*P value was calculated by one-way ANOVA with Tukey's correction or Chi-square test

ACE angiotensin converting enzyme inhibitor, ANOVA analysis of variance, ARB angiotensin receptor blocker, BMI body mass index, BSA body surface area, DBP diastolic blood pressure, DCM dilated cardiomyopathy, HR heart rate, MR mitral regurgitation, SBP systolic blood pressure

**Table 2** Comparison of CMR parameters

	DCM MR (+), N = 22	DCM MR (-), N = 18	Controls, N = 20	* P-value DCM MR (+) vs DCM MR (-)	* P-value DCM MR (+) vs Controls	* P-value DCM MR (-) vs Controls
Cine MRI parameters						
EDVI, mL/m <sup>2</sup>	129 ± 43	122 ± 36	80 ± 16	0.79	<0.05	<0.05
ESVI, mL/m <sup>2</sup>	89 ± 43	84 ± 36	32 ± 10	0.86	<0.05	<0.05
SVI, mL/m <sup>2</sup>	40 ± 11	38 ± 10	48 ± 10	0.86	0.04	0.02
LVEF, %	34 ± 13	33 ± 11	61 ± 4	0.98	<0.05	<0.05
LVMI, g/m <sup>2</sup>	67 ± 23	68 ± 17	46 ± 9	0.99	<0.05	<0.05
RVEF, %	52 ± 10	52 ± 14	58 ± 5	1.00	0.15	0.18
LA dimension, mm	58 ± 9	55 ± 7	52 ± 9	0.59	0.06	0.41
LA area (2 chamber view), cm <sup>2</sup>	29 ± 9	25 ± 6	-	0.21	-	-
LA area (4 chamber view), cm <sup>2</sup>	28 ± 9	23 ± 6	-	0.07	-	-
LA volume (ml)	125 ± 54	92 ± 31	-	0.04	-	-
RA dimension, mm	51 ± 10	52 ± 9	55 ± 9	0.98	0.42	0.58
LGE findings						
LV LGE	3 (15 %)	5 (27 %)	0 (0 %)	0.27	0.09	0.01
Papillary muscle LGE	0 (0 %)	0 (0 %)	0 (0 %)	-	-	-

\*P value was calculated by one-way ANOVA with Tukey's correction or Chi-square test

ANOVA analysis of variance, CMR cardiovascular magnetic resonance, DBP diastolic blood pressure, DCM dilated cardiomyopathy, EDV end-diastolic volume, EDVI end-diastolic volume index, EF ejection fraction, ESV end-systolic volume, ESVI end-systolic volume index, HR heart rate, LGE late gadolinium enhancement, LV left ventricle, LVMI left ventricular mass index, MR mitral regurgitation



in DCM patients compared to control subjects. LA volume was significantly higher in DCM patients with MR compared to those without MR ( $p = 0.04$ ). LGE of LV myocardium was observed in 8 of 40 (20 %) DCM patients, while no DCM patients had LGE of the papillary muscles. Healthy control subjects did not show any LGE in the LV or the papillary muscles. Table 3 shows comparison of papillary muscle parameters. Papillary muscle was significantly thicker, longer in DCM patients in comparison to healthy controls. Regarding mitral annulus diameter, papillary muscle shortening and tenting height, significant difference was also observed between DCM patients with mitral regurgitation and those without mitral regurgitation. Table 4 summarizes the intra- and inter-observer variability for measurement of papillary muscle size. Intra class correlation coefficients for papillary muscle size measurement were  $>0.80$  both for intra- and inter-observer variability.

#### Comparison of papillary muscle $T_1$ time between cardiomyopathy and healthy control subjects

Figure 3 illustrates individual papillary muscle and LV  $T_1$  time for 3 groups. Mean anterior papillary muscle  $T_1$  time was  $1127 \pm 36$  msec for DCM with mitral regurgitation ( $p < 0.05$  vs DCM without mitral regurgitation;  $p < 0.05$  vs healthy controls),  $1063 \pm 16$  msec for DCM without mitral regurgitation ( $p = 0.29$  vs healthy controls) and  $1051 \pm 20$  msec for healthy controls. Mean posterior papillary muscle  $T_1$  time was  $1124 \pm 30$  msec for DCM with mitral

regurgitation ( $p < 0.05$  vs DCM without mitral regurgitation;  $p < 0.05$  vs healthy controls),  $1062 \pm 19$  msec for DCM without mitral regurgitation ( $p = 0.51$  vs healthy controls) and  $1053 \pm 25$  msec for healthy controls. LV native  $T_1$  time was significantly elevated in DCM patients in comparison to healthy controls ( $p < 0.05$ , Fig. 3), but similar between DCM patients with mitral regurgitation and those without mitral regurgitation ( $1129 \pm 38$  msec vs  $1134 \pm 58$  msec,  $p = 0.93$ ). Figure 4 demonstrates regional LV native  $T_1$  time in each segments. There was no substantial variability across 16 segments both in DCM patients and controls. In addition, there was no significant correlation between papillary muscle  $T_1$  time and mid-level LV  $T_1$  time ( $r = 0.31$ ,  $p = 0.05$  by Spearman's correlation coefficient). There was no significant difference in  $T_1$  time between base, mid and apical slices (base,  $1125 \pm 52$  msec; mid,  $1130 \pm 47$  msec; apex,  $1138 \pm 54$  msec,  $p = 0.53$  by one-way ANOVA). Figure 5 shows the relationship between papillary muscle  $T_1$  time and papillary muscle morphology. Elevated papillary muscle  $T_1$  time was associated with increased papillary muscle diameter, increased papillary muscle length and decreased papillary muscle shortening.

#### Relationship between papillary muscle $T_1$ time and mitral regurgitant fraction

Figure 6 shows the relationship between papillary muscle  $T_1$  time and mitral regurgitant fraction in DCM patients. Mitral regurgitant fraction was significantly correlated

**Table 3** Comparison of papillary muscle related parameters

	DCM MR (+), $N = 22$	DCM MR (-), $N = 18$	Controls, $N = 20$	* $P$ -value DCM MR (+) vs DCM MR (-)	* $P$ -value DCM MR (+) vs Controls	* $P$ -value DCM MR (-) vs Controls
Maximum anterior PAP diameter, mm	$11.6 \pm 3.3$	$10.2 \pm 1.5$	$7.9 \pm 1.3$	0.14	$<0.05$	$<0.05$
Minimum anterior PAP diameter, mm	$7.9 \pm 1.9$	$7.6 \pm 1.4$	$6.8 \pm 0.5$	0.73	$<0.05$	0.19
Maximum posterior PAP diameter, mm	$10.6 \pm 3.1$	$9.3 \pm 1.5$	$7.0 \pm 0.6$	0.14	$<0.05$	$<0.05$
Minimum posterior PAP diameter, mm	$6.9 \pm 1.7$	$7.1 \pm 0.9$	$5.0 \pm 0.5$	0.79	$<0.05$	$<0.05$
Maximum anterior PAP length, mm	$44.7 \pm 7.6$	$42.3 \pm 6.3$	$34.5 \pm 2.8$	0.42	$<0.05$	$<0.05$
Minimum anterior PAP length, mm	$37.6 \pm 6.8$	$31.6 \pm 5.4$	$23.5 \pm 2.9$	$<0.05$	$<0.05$	$<0.05$
Maximum posterior PAP length, mm	$40.9 \pm 8.4$	$37.8 \pm 5.8$	$32.9 \pm 3.1$	0.28	$<0.05$	$<0.05$
Minimum posterior PAP length, mm	$33.7 \pm 7.3$	$27.9 \pm 3.5$	$22.6 \pm 3.1$	$<0.05$	$<0.05$	$<0.05$
Anterior PAP shortening, %	$15.8 \pm 4.4$	$25.5 \pm 4.1$	$32.0 \pm 4.8$	$<0.05$	$<0.05$	$<0.05$
Posterior PAP shortening, %	$17.7 \pm 5.8$	$26.0 \pm 3.4$	$31.5 \pm 4.9$	$<0.05$	$<0.05$	$<0.05$
Mitral annulus (4chamber), mm	$37.8 \pm 6.6$	$32.5 \pm 3.8$	$28.7 \pm 1.1$	$<0.05$	$<0.05$	$<0.05$
Mitral annulus (2chamber), mm	$38.5 \pm 4.5$	$34.2 \pm 5.1$	$31.6 \pm 2.0$	$<0.05$	$<0.05$	$<0.05$
Tenting height, mm	$10.3 \pm 1.1$	$6.1 \pm 1.7$	$2.7 \pm 1.3$	$<0.05$	$<0.05$	$<0.05$
Anterior mitral leaflet length, mm	$23.6 \pm 3.5$	$19.9 \pm 2.3$	$21.7 \pm 1.6$	$<0.05$	0.06	0.11
Posterior mitral leaflet length, mm	$13.9 \pm 4.0$	$12.6 \pm 1.9$	$10.4 \pm 1.4$	0.27	$<0.05$	$<0.05$

\* $P$  value was calculated by one-way ANOVA with Tukey's correction

ANOVA analysis of variance, DCM dilated cardiomyopathy, MR mitral regurgitation, PAP papillary muscle

**Table 4** Intra- and inter-observer variability for measurement of papillary muscle size

	Intra observer variability		Inter observer variability	
	ICC	95 % CI	ICC	95 % CI
Maximum papillary muscle diameter	0.93	0.84–0.97	0.92	0.81–0.97
Minimum papillary muscle diameter	0.87	0.69–0.94	0.82	0.61–0.93
Maximum papillary muscle length	0.91	0.78–0.96	0.88	0.73–0.95
Minimum papillary muscle length	0.91	0.78–0.96	0.86	0.70–0.95

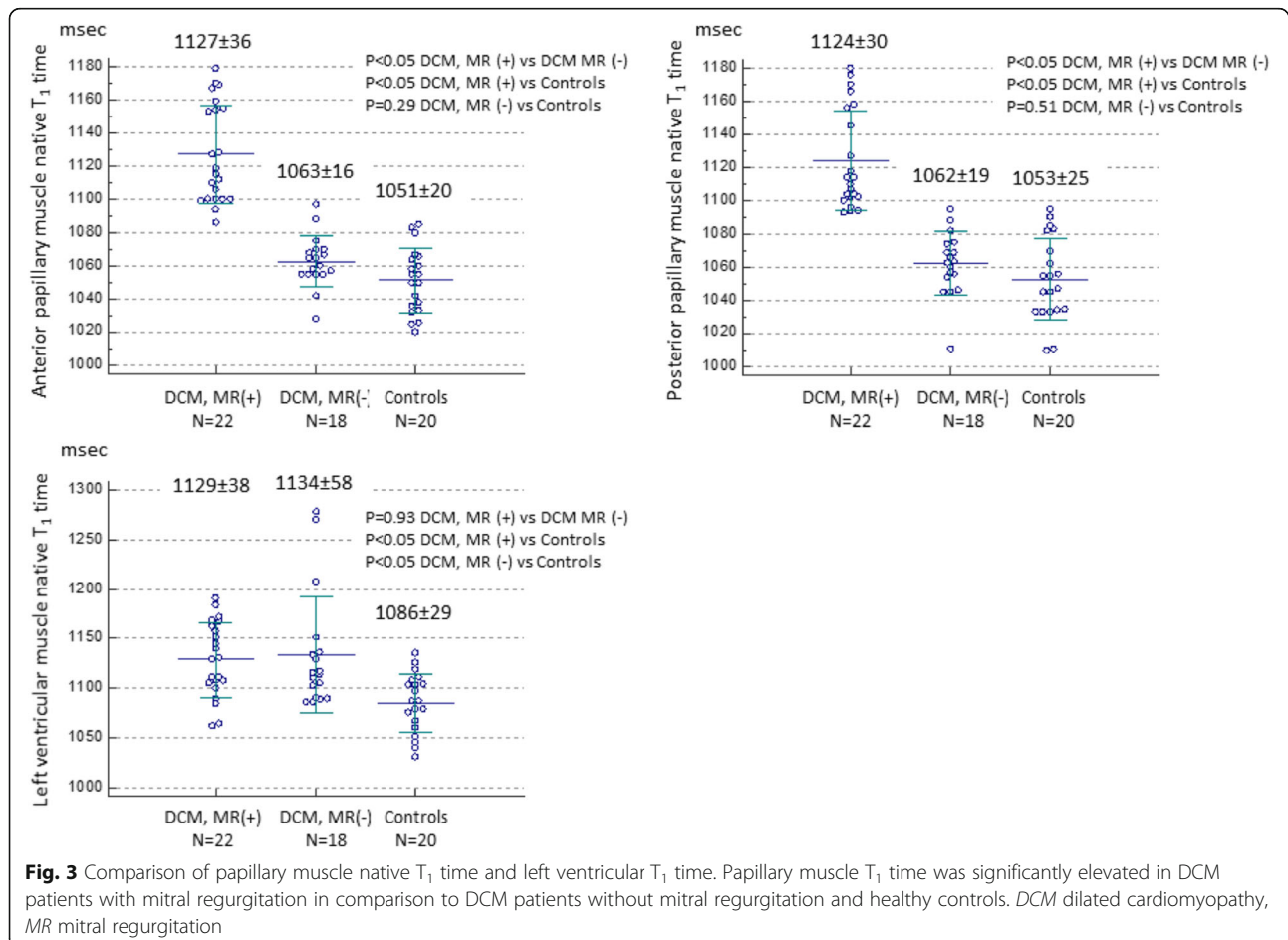
CI confidence interval, ICC intra class correlation coefficients

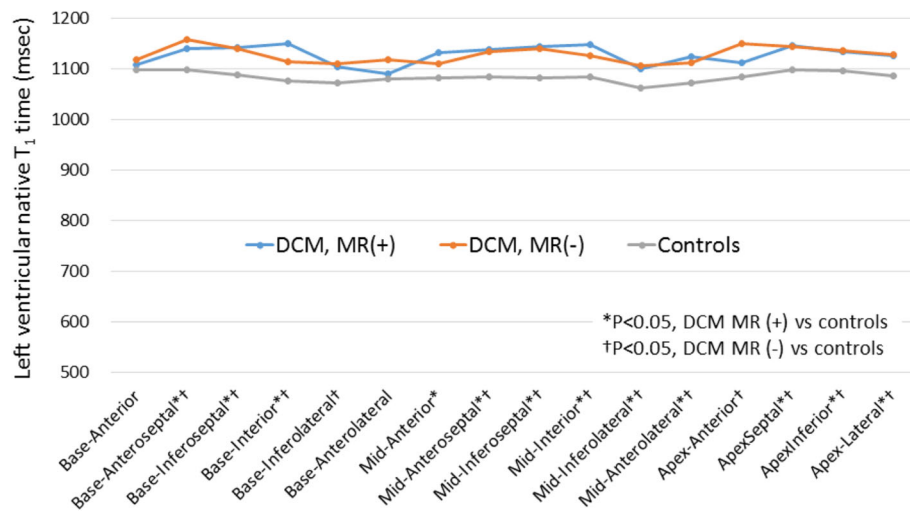
with both anterior and posterior papillary muscle  $T_1$  time ( $p < 0.05$ ) but not with LV myocardial  $T_1$  time ( $p = 0.67$ ). Table 5 summarizes the results of multivariate linear regression analysis for determinants of mitral regurgitant fraction in all DCM patients ( $n = 40$ ). In the multivariate analysis, average of anterior and posterior papillary muscle native  $T_1$  time was employed for analysis. Multivariate linear regression analysis identified papillary muscle native  $T_1$  time ( $\beta = 0.10$ , 95 % CI: 0.03–0.17,  $p < 0.05$ ) as an independent determinant of mitral regurgitant fraction. Table 6 shows the results of multivariate linear regression analysis for determinants of mitral regurgitant fraction in

DCM patients with MR ( $n = 22$ ). Multivariable linear regression analysis identified posterior papillary muscle maximum diameter ( $\beta = 1.32$ , 95 % CI: 0.50–2.16,  $p < 0.05$ ) and papillary muscle native  $T_1$  time ( $\beta = 0.11$ , 95 % CI: 0.03–0.20,  $p < 0.05$ ) as independent determinants of mitral regurgitant fraction.

#### Variability of papillary muscle $T_1$ measurement

Repeatability coefficients of anterior papillary muscle  $T_1$  time were 2.0 % for intra-observer variability, 4.1 % for inter-observer variability. Repeatability coefficients of posterior papillary muscle native  $T_1$  time were 1.3 % for



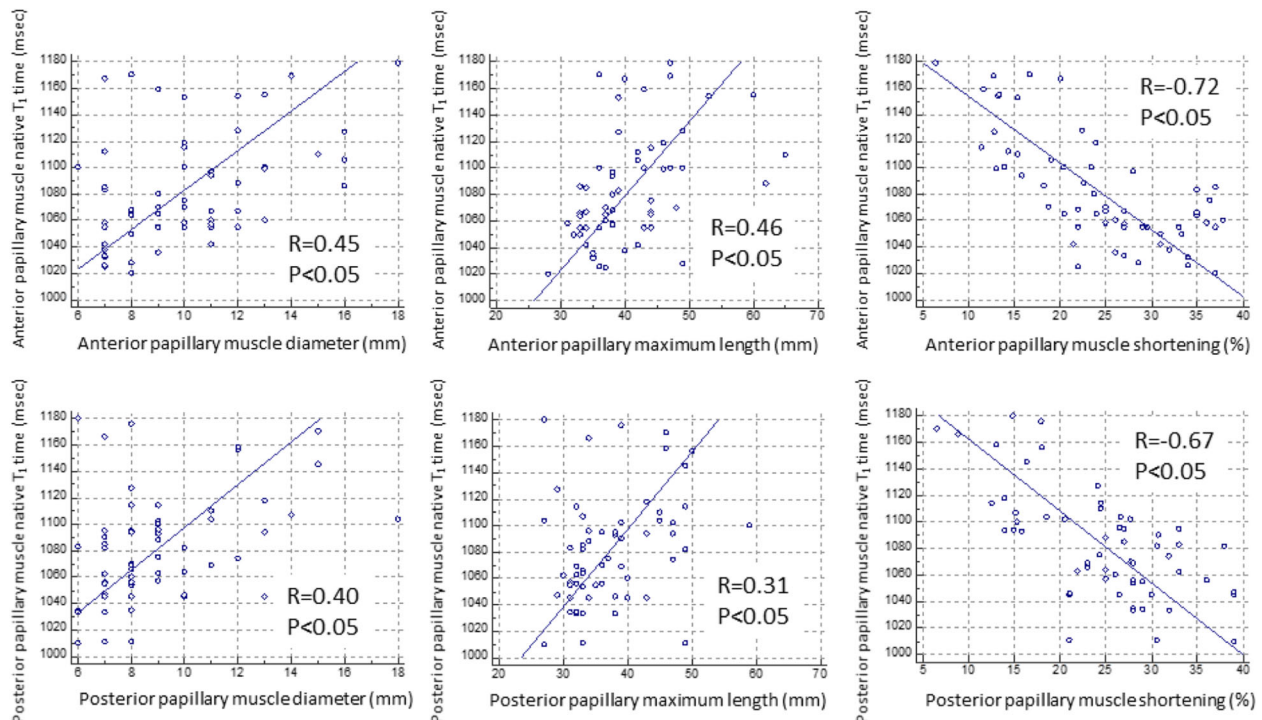


**Fig. 4** Regional left ventricular native  $T_1$  time in each segments. There was no substantial variability across 16 segments both in DCM patients and controls. DCM dilated cardiomyopathy, MR mitral regurgitation

intra-observer variability, 5.0 % for inter-observer variability. Variability of papillary muscle native  $T_1$  time measurement was high (CV of intra-observer variability: 0.9 % for anterior papillary muscle and 0.7 % for posterior papillary muscle; CV of inter-observer variability: 1.6 % for anterior papillary muscle and 1.8 % for posterior papillary muscle).

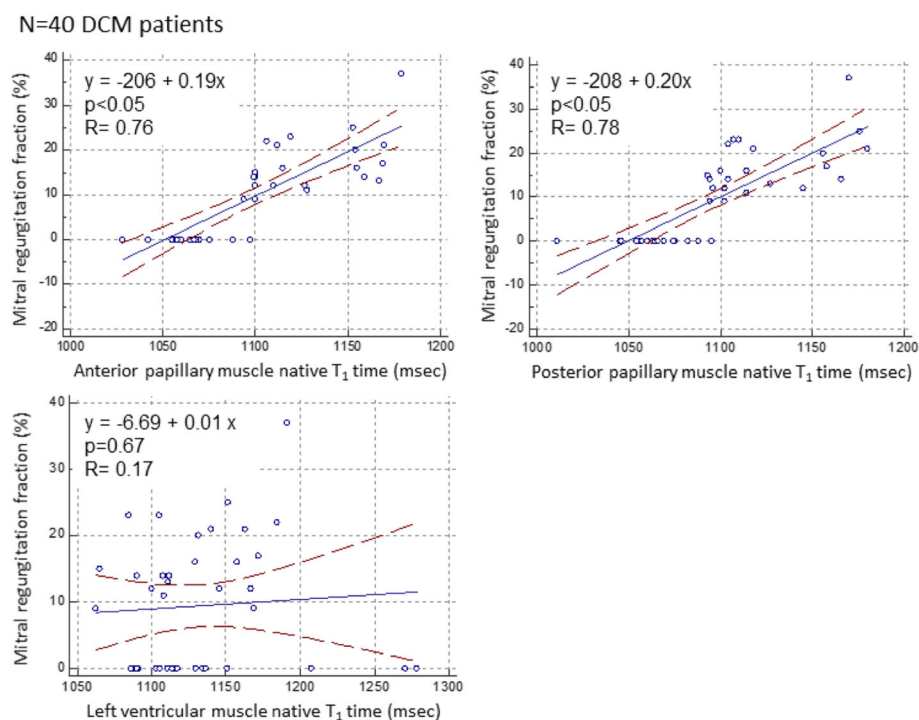
## Discussion

To the best of our knowledge, this study is the first investigation to examine the feasibility and variability of papillary muscle native  $T_1$  time measurement, and to investigate the relationship between papillary muscle  $T_1$  time and severity of functional mitral regurgitation in DCM patients. We found a significant difference of papillary muscle native  $T_1$



**Fig. 5** Relationship between papillary muscle native  $T_1$  time and morphology. Papillary muscle native  $T_1$  time was correlated with papillary muscle diameter, length and shortening





**Fig. 6** Relationship between papillary muscle native  $T_1$  time and mitral regurgitant fraction. Papillary muscle native  $T_1$  time was associated with mitral regurgitant fraction in DCM patients. DCM dilated cardiomyopathy

**Table 5** Univariate and multivariate linear regression analysis for determinants of mitral regurgitant fraction in all DCM patients ( $n = 40$ )

	Univariable analysis			Multivariable analysis		
	B	95 % CI for $\beta$	P-value	B	95 % CI for $\beta$	P-value
Age, year	-0.01	-0.20-0.18	0.90	-	-	-
Gender, male	-3.99	-10.50-2.53	0.22	-	-	-
Body mass index, kg/m <sup>2</sup>	0.22	-0.21-0.71	0.28	-	-	-
LVEDVI, mL/m <sup>2</sup>	0.05	-0.02-0.12	0.18	-	-	-
LVEF, %	-0.16	-0.40-0.07	0.17	-	-	-
LVMl, g/m <sup>2</sup>	0.06	-0.08-0.20	0.37	-	-	-
Left atrial area (4 chamber), cm <sup>2</sup>	0.56	0.23-0.91	<0.05	0.17	-1.05-1.39	0.25
Left atrial area (2 chamber), cm <sup>2</sup>	0.36	-0.16-0.89	0.17	-	-	-
Left atrial volume, cm <sup>3</sup>	0.10	0.04-0.16	<0.05	-0.01	-0.21-0.20	0.95
Mitral annulus (4 chamber), mm	0.43	-0.01-0.87	0.06	-	-	-
Tenting height, mm	2.28	1.38-3.17	<0.05	0.61	-0.37-1.59	0.21
Anterior papillary muscle maximum diameter, mm	1.28	0.34-2.23	<0.05	0.29	-0.59-1.16	0.51
Posterior papillary muscle maximum diameter, mm	1.37	0.35-2.38	<0.05	0.73	-0.23-1.68	0.13
Anterior papillary muscle shortening, %	-0.87	-1.20- -0.54	<0.05	-0.10	-0.68-0.49	0.74
Posterior papillary muscle shortening, %	-0.92	-1.24- -0.60	<0.05	-0.21	-0.75-0.32	0.42
Papillary muscle $T_1$ time, sec	0.16	0.12-0.21	<0.05	0.10	0.03-0.17	<0.05

Variables with  $p$  value < 0.05 in univariate analysis were included in multivariable analysis

CI confidence interval, DCM dilated cardiomyopathy, LVEDVI left ventricular end-diastolic volume index, LVEF left ventricular ejection fraction, LVMl left ventricular mass index, MR mitral regurgitation

**Table 6** Univariate and multivariate linear regression analysis for determinants of mitral regurgitant fraction in DCM patients with MR ( $n = 22$ )

	Univariable analysis			Multivariable analysis		
	B	95 % CI for $\beta$	P-value	B	95 % CI for $\beta$	P-value
Age, year	0.08	-0.11–0.26	0.41	-	-	-
Gender, male	-0.49	-6.85–5.86	0.87	-	-	-
Body mass index, kg/m <sup>2</sup>	0.17	-0.29–0.64	0.44	-	-	-
LVEDVI, mL/m <sup>2</sup>	0.05	-0.02–0.11	0.17	-	-	-
LVEF, %	-0.17	-0.40–0.05	0.12	-	-	-
LVMI, g/m <sup>2</sup>	0.06	-0.06–0.20	0.28	-	-	-
Left atrial area (4 chamber), cm <sup>2</sup>	0.34	0.01–0.68	<0.05	0.13	-0.24–0.30	0.85
Left atrial area (2 chamber), cm <sup>2</sup>	0.14	-0.21–0.49	0.42	-	-	-
Left atrial volume, cm <sup>3</sup>	0.05	-0.01–0.11	0.08	-	-	-
Mitral annulus (4 chamber), mm	-0.05	-0.50–0.41	0.83	-	-	-
Tenting height, mm	1.46	-1.09–4.01	0.24	-	-	-
Anterior papillary muscle maximum diameter, mm	0.64	-0.22–1.51	0.14	-	-	-
Posterior papillary muscle maximum diameter, mm	0.93	0.05–1.82	<0.05	1.32	0.50–2.16	<0.05
Anterior papillary muscle shortening, %	0.31	-1.12–0.21	0.17	-	-	-
Posterior papillary muscle shortening, %	-0.51	-0.97–0.05	<0.05	-0.17	-0.58–0.23	0.41
Papillary muscle T <sub>1</sub> time, sec	0.11	0.02–0.20	<0.05	0.11	0.03–0.20	<0.05

Variables with  $p$  value < 0.05 in univariate analysis were included in multivariable analysis

CI confidence interval, DCM dilated cardiomyopathy, LVEDVI left ventricular end-diastolic volume index, LVEF left ventricular ejection fraction, LVMI left ventricular mass index, MR mitral regurgitation

time between DCM patients with mitral regurgitation and those without mitral regurgitation, a correlation between papillary muscle native T<sub>1</sub> time and mitral regurgitant fraction in DCM patients and low variability of papillary muscle T<sub>1</sub> time measurement.

#### Papillary muscle T<sub>1</sub> time and papillary muscle morphology in DCM patients

Previous echocardiographic studies have shown that the papillary muscle dysfunction is observed in several cardiovascular diseases. Papillary muscle shortening has been assessed using transthoracic echocardiography and used as a functional parameter [24, 25]. In myocardial infarction patients, papillary muscle function was substantially reduced compared to healthy controls (papillary muscle shortening:  $15 \pm 14\%$  vs  $30 \pm 8\%$ ) [25]. Reduced papillary muscle shortening has also been reported in cardiomyopathy patients including hypertrophic cardiomyopathy or DCM [24, 26]. In the current study, we measured papillary muscle diameter, length and shortening using cine CMR and showed that papillary muscle shortening was significantly reduced in DCM patients in comparison to healthy controls. This absolute value and difference findings were consistent with previous echocardiographic studies. In addition, we found a significant difference in papillary muscle shortening between DCM patients with mitral regurgitation in

comparison to those without mitral regurgitation, suggesting that papillary muscle dysfunction may be contributing to mitral regurgitation.

The maximum papillary muscle diameter was approximately 7 mm in healthy controls and 10 mm in DCM patients. Elevated papillary muscle native T<sub>1</sub> time was associated with larger diameter, longer length, decreased shortening in DCM patients. This finding suggested that papillary muscle T<sub>1</sub> time might reflect papillary muscle pathological changes in DCM patients (i.e. papillary muscle fibrosis). Furthermore, papillary muscle native T<sub>1</sub> time was increased in DCM patients with mitral regurgitation compared to those without mitral regurgitation, but LV native T<sub>1</sub> time was similar between 2 groups. These results suggest that the papillary muscle native T<sub>1</sub> time may be a more sensitive for the mechanical stress induced by functional mitral regurgitation. A previous study by Okayama et al. showed that LGE evidence of bilateral papillary muscle infarction correlated with LV remodeling and functional mitral regurgitation [27]. Although the assessment of papillary muscle abnormality is feasible by LGE, an important advantage of non-contrast native T<sub>1</sub> mapping is the ability to evaluate papillary muscle abnormality in patients with renal dysfunction who are at high risk of systemic nephrogenic fibrosis [28]. In addition, we did not observe any papillary muscle LGE in this study, suggesting that the papillary muscle pathological change is *diffuse* rather than *focal* in DCM patients.

### Clinical implication

We found significant difference in papillary muscle native  $T_1$  time between DCM patients with mitral regurgitation and those without mitral regurgitation. However, no significant difference was found in LV native  $T_1$  time. In addition, papillary muscle  $T_1$  time was independently correlated with severity of functional mitral regurgitation after adjustment of conventional determinants, including tenting height, mitral annulus diameter. Previous transthoracic echocardiographic studies showed that tenting height is a strong indicator of effective orifice area in patients with LV dysfunction and functional mitral regurgitation [29]. Further study is necessary to elucidate if papillary muscle native  $T_1$  time has prognostic value in DCM patients.

### Study limitations

Our study has several limitations. The sample size was modest and the study population was limited to DCM patients and healthy controls. Our  $T_1$  mapping sequence, STONE, has not been histologically validated for papillary muscle  $T_1$  mapping. Therefore, we do not know the true cause of the elevated papillary muscle native  $T_1$  time in DCM patients. Although  $T_1$  mapping images acquired by STONE were motion corrected, relatively low spatial resolution of  $T_1$  mapping images and the partial volume effect are not negligible for  $T_1$  measurement of papillary muscle. To avoid partial volume effect with blood pool, we've carefully placed the ROI on papillary muscle much smaller than actual papillary muscle diameter not to include the pixels from LV blood pool. As shown on Fig. 2, size of ROI on papillary muscle was much smaller than actual size of papillary muscle. The pixel size of ROI drawn on papillary muscle was 16–40 pixels. It would be also interesting to investigate the relationship between papillary muscle extracellular volume (ECV) and mitral regurgitant fraction. However, calculation of ECV requires registration between native and post-contrast  $T_1$  images, which will be challenging for a mobile and small papillary muscle anatomy. Regarding LV ECV, in our cohort, there were 21 DCM patients and 9 controls with ECV data. Significant difference was found between DCM patients and controls in LV ECV averaged over 16 segments ( $0.30 \pm 0.04$  vs  $0.27 \pm 0.02$ ,  $p = 0.03$ ). However, no significant difference was found between DCM patients with MR and those without MR ( $0.31 \pm 0.05$  vs  $0.29 \pm 0.04$ ,  $p = 0.63$ ). A larger, more diverse study is required to assess the clinical relevance of papillary muscle native  $T_1$  time. Because this study is a cross-sectional study, we can't say any causal relationship between papillary muscle  $T_1$  time and functional mitral regurgitation. Examination of the potential difference of the time course of  $T_1$  change in the myocardium and papillary muscle would also be of interest, but is beyond the scope of this study.

### Conclusions

Measurement of papillary muscle native  $T_1$  time is both feasible and reproducible. This CMR approach successfully detects abnormal papillary muscle native  $T_1$  time in DCM patients with functional mitral regurgitation.

### Abbreviations

ANOVA: Analysis of variance; ARCTIC: Adaptive registration of varying contrast-weighted images for improved tissue characterization; CI: Confidence interval; CMR: Cardiovascular magnetic resonance; CV: Coefficient of variation; DCM: Dilated cardiomyopathy; ECV: Extracellular volume; FA: Flip angle; FOV: Field of view; LA: Left atrial; LGE: Late gadolinium enhancement; LV: Left ventricular; MR: Mitral regurgitation; ROI: Region of interest; SD: Standard deviation; SENSE: Sensitivity encoding; SSFP: Steady-state free precession; STONE: Slice-interleaved  $T_1$ ; TE: Echo time; TFE: Turbo field echo; TR: Repetition time

### Acknowledgements

Not applicable.

### Funding

Shingo Kato, MD receives scholarship from Banyu Life Science Foundation International. Reza Nezafat, PhD receives grant support from NIH R01EB008743, R21HL127650, R01HL129185, AHA 15EIA22710040 and Samsung Electronics.

### Availability of data and materials

Not applicable.

### Authors' contributions

Author contribution are as following; conception and design (SK, SR, TB, SB, KVK, BG, WJM, RN), analysis and interpretation of data (SK, SA, SN, SR, JJ), drafting (SK, SR), revising (SK, SN, FND, WJM, RN). All authors read and approved the final manuscript.

### Authors' information

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

### Consent for publication

All participants in this study gave written informed consent to participate and to publish.

### Ethics approval and consent to participate

The study was approved by the Beth Israel Deaconess Medical Center Institutional Ethics Committee, and all subjects gave written informed consent to participate and to publish.

### Author details

<sup>1</sup>Department of Medicine (Cardiovascular Division), Beth Israel Deaconess Medical Center and Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA. <sup>2</sup>Department of Radiology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA. <sup>3</sup>Department of Cardiology, Yokohama City University Hospital, Yokohama, Japan. <sup>4</sup>Biomedical Engineering Department, King's College London, London, UK. <sup>5</sup>Biomedical Engineering Department, Cairo University, Giza, Egypt.

Received: 21 July 2016 Accepted: 29 October 2016

Published online: 16 November 2016

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